Claims

1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of
   - selecting a target nucleic acid, if necessary elucidating its sequence
   - generating the antisense oligonucleotide with the proviso that
     - the oligonucleotide comprises at least 8 residues,
     - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,
     - the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
     - the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
     - the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} \geq 0.29$$

   - and synthesizing the oligonucleotide thus generated in a per se known manner.

2. The method according to claim 1, wherein the generated oligonucleotide complies with the following specification

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} = 0.33 \text{ to } 0.86$$

3. The method according to ~~any one of the claims 1 or 2,~~ Claim 1 wherein the generated oligonucleotides are modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.

4. The method according to claim 3, wherein the generated oligonucleotides are modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

5. The method according to claim 3 ~~and/or 4~~, wherein the oligonucleotide has at least two different types of modifications.

6. The method according to ~~any one of the claims 1 to 5,~~ Claim 1 wherein the oligonucleotides are reacted with folic acid, hormones such as steroid hormones or cortico-steroides or derivatives thereof by linking the oligo-nucleotides covalently to or mixing with folic acid, hormones such as steroide hormones or corticosteroides, peptides, proteoglycans, glycolipids or phospholipids.

7. An antisense oligonucleotide or derivative thereof obtainable according to the method according to any one of the claims 1 to 6 except oligonucleotides represented by Fig. 4.

8. The oligonucleotide or derivative of claim 7, which does not contain four or more consecutive guanosine (N_aGGGGN_b) or inosine (N_aIIIIN_b) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two ore more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$), wherein N_a, N_b, N_c represent indepently nucloetides or oligonucleotides or derivatives thereof having 0 to 20 residues.

9. The oligonucleotide or derivative of claims 7 and/or 8, comprising a minimum of ten elements and a maximum of 24 elements capable of forming either two or three hydrogen bonds per element.

10. The oligonucleotide or derivative according to any one of the claims 7 to 9, having modifications at the bases, the sugars or the phosphate moieties of the oligonucleotides.

11. The oligonucleotide or derivative of any one of the claims 7 to 10, wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

12. The oligonucleotide or derivative of any one of the claims 7 to 11 coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

13. The oligonucleotide according to any one of the claims 7 to 12, wherein the antisense oligonucleotide against the TGF-ß1 gene comprise the sequences 41 to 73 of Fig. 3, the oligonucleotides against the gene p53 comprising the sequences 74 to 106 of Fig. 3, the antisense oligonucleotides against junB comprising the sequences 154 to 172 of Fig. 3, the antisense oligonucleotides against junD comprising the sequences 173 to 203 of Fig. 3, the antisense oligonucleotides against the erbB-2 gene comprise the sequences 298 to 380 of Fig 3, the antisense oligonucleotides against c-fos genes comprise the sequences 476 - 506 of Fig. 3; the antisense oligonucleotides against the gene TGF-ß2 comprise the sequences 519 to 556 of Fig. 3 as well as the antisense oligonucleotides against the gene rb comprise the sequences 597 to 641 of Fig. 3.;
as well as sequences 1273 to 1764. of Fig. 5.

14. A composition comprising an oligonucleotide or derivative according to any one of the claims 7 to 13 for the manufacturing of a medicament or a composition for the inhibition of the genes p53, rb, junD, junB, TGF-ß1, TGF-ß2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells.

15. A medicament comprising an oligonucleotide according to any one of the claims 7 to 13 together with additives.

16. The use of the oligonucleotides according to any of the claims 7 to 13 for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases, and/or metabolic dysfunctions.

17. The use of the oligonucleotides according to any one of the claims 7 to 13 for the analysis of gene function or drug target validation.

add D'

add E'